Appropriate Control Strategies Eliminate the Need for Redundant Testing of Pharmaceutical Products

Key Messages

Importation quality control testing for pharmaceutical, biological/biotechnology and vaccine products at the country level is unlikely to increase public health protection, can delay batch release and therefore access to life saving medicines, and creates an unnecessary burden for the global pharmaceutical industry.

1. Pharmaceutical, biological/biotechnology and vaccine manufacturers have established appropriate control over the production of products through in-process controls, validation of the manufacturing process and release testing of the finished drug products, in line with internationally recognized current good manufacturing practice (GMP) standards.

2. Robust quality systems are in place guiding manufacturing and distribution practices including appropriate validation, control and risk management strategies for the handling, storage, transportation and distribution of the finished drug products.

3. The adequacy of a manufacturer’s quality oversight is ensured through reporting requirements as well as regular inspections by competent health authority inspectorates confirming the adequacy of the established processes and the compliance with the product license.

4. National requirements to undertake such redundant importation testing unnecessarily increases inventories, delays product distribution and patient access to high quality, safe and efficacious life saving therapeutic and preventative medicines.

5. Regulatory Authorities may use a risk-based approach, by assessing regular and satisfactory inspection results of the Quality Control facilities, to determine whether elimination of redundant importation testing is warranted.

For these reasons, this type of importation testing is considered redundant, in many cases, and should not be required in all circumstances.
**Background**

To help in ensuring drug product quality and safety, health authorities in many countries have implemented, or are considering implementing, redundant quality control testing requirements for pharmaceuticals, biological/biotechnology and vaccine products entering their countries. Historically such redundant testing requirements may have been necessary to prevent the distribution of unsafe or non-conforming drug product. However, today, pharmaceutical, vaccine, and the biotechnology industries have developed and implemented robust quality systems to ensure the identity, safety, purity and potency of its drug products throughout its manufacture and international distribution channels, thereby eliminating the need for this redundant testing.

This position paper highlights the scientific and regulatory basis for not requiring redundant importation testing and notes the problems with this practice; including the potential for significant delays in supplying lifesaving therapeutic and preventative medicines to patients.

**Sound Science, Product Knowledge and Good Practices**

Recognizing that there may have been gaps in the past, modern manufacturers of pharmaceuticals have adequate control over the production of their products through more advanced process understanding, proper in-process controls, extensive process and product validation efforts, advances in analytical techniques and sophisticated change control systems. These control strategies extend beyond the manufacturer’s own facility by validating e.g. the cold chain including the impact of potential temperature excursions on the shelf-life specifications of the drug product. Also the distribution of the products is well controlled by implementing, for example, serialization and tamper evidence measures. All these measures ensure the compliance of the drug product to its registered specifications throughout the entire lifecycle from the time of production in the exporting country through the importation, storage and distribution of the product in the importing country.

Understanding the value of these holistic control strategies, several global health authorities, including the Brazilian Authority (ANVISA) and the U.S. Food and Drug Administration (FDA) have eliminated redundant testing for certain biological products, including rDNA-derived and monoclonal antibody biotechnology products. Likewise, China (SFDA) has eliminated redundant importation testing for small molecules.

When discussing its policy change to eliminate redundant testing (lot-to-lot release), FDA regulators determined that “once a company has demonstrated its ability to consistently produce acceptable lots, it is not necessary for FDA to verify that each manufactured lot is acceptable for release.” [1] The Agency also noted that eliminating this testing requirement would result in “significant savings of time and resources for both the industry and agency” without adding any “significant risk to public health.” [2]

**Recognised Regulatory Oversight**

Extensive regulatory oversight through regular health authority inspections confirms the adequacy of a manufacturer’s quality systems and thus compliance with the product’s release specifications registered in the respective countries.
Several recent reports, including the presentation to the World Health Organization (WHO) on behalf of IFPMA [3] highlight that inspections across the globe have increased in the last decade as more and more countries begin to regulate pharmaceutical, biological/biotechnology and vaccine products in their jurisdiction. The rationale for conducting inspections is to give regulatory agencies confidence that a manufacturing site, the relevant quality system and its related processes are under control and thus able to manufacture safe products of high quality according to licensed requirements and specifications. As a result, manufacturing practices and product release procedures including release testing are under more scrutiny by regulatory agencies than ever before. In addition, the increasing requirements for annual reporting, adverse event reporting, and the increased communication between health authorities give regulators much greater confidence in a manufacturer’s practices and quality systems.

Furthermore, many industry groups (e.g. PDA [4], ISPE, EFPIA), health authorities and global organizations complemented by regulators (e.g. PIC/S, WHO, ICH, ASEAN, APEC) have worked together to harmonize and standardize the medicinal products approval and control process as well as GMPs. Because of these harmonization efforts, submission and manufacturing practices across the globe are becoming more standardized allowing greater information flow and understanding of risks between regulatory agencies.

**Repeated Testing: Challenges and Issues**

1. Not surprisingly, repeated testing at importation takes significant time and effort and may result in a lack of access or delayed access of medicines to patients. In addition, the time taken to locally test and release a batch of product may effectively shorten the time the product is able to be distributed before its expiry date is reached. Consideration should also be given to the time consumed in the event of a false out of specification result, thus potentially causing product shortages and stock outs.

2. Additional product testing may be expensive, difficult to implement and to perform especially for biotechnology products and vaccines. Consequently, where government testing is required, each country will need to allocate significant resources for equipment and personnel to perform this testing, which may be extremely complex given the nature of many assays (e.g. biological potency assays). Further, government laboratories may not have the proper equipment and biological-originated materials (e.g. indicator cell, antibody) or be able to perform the testing, as many of these assays are subject to variation if not accompanied by a proper analytical method technology transfer to the receiving laboratory.

3. Redundant importation testing may also result in significant supply chain issues for a country, including product inventory and sample management problems. Moreover, a less stringent chain of custody for test samples may increase the risk for samples to be lost or diverted. This risk is minimized when robust good distribution practices (GDPs) are not interrupted [5]. Thus, the complexity in product supply chain and less stringent chain of custody for test samples may lead to an increased risk to patients.
Conclusions

In many cases, importation testing is redundant. Therefore, under circumstances where a manufacturer or a manufacturing facility of a pharmaceutical, biological/biotechnology or vaccine product:

- provides evidence that their product manufacturing, testing and storage/distribution systems are well controlled and validated;
- has implemented a proper quality system to assure compliance; and
- is under regular control of globally recognized inspectorates (e.g. PIC/S members) or the inspectorates of other competent regulatory authorities (e.g. WHO CPP procedure [6])

then, there should be confidence by the importing country’s Health Authority that the product is safe, efficacious and complies with registered specifications. As a consequence, the manufacturer should be given the opportunity to obtain a waiver for redundant, importation testing.

References

About IFPMA

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry’s 1.3 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

IFPMA manages global initiatives including: IFPMA Developing World Health Partnerships studies and identifies trends for the research-based pharmaceutical industry’s long-term partnership programs to improve health in developing countries, IFPMA Code of Practice sets standards for ethical promotion of medicines, IFPMA Clinical Trials Portal helps patients and health professionals find out about ongoing clinical trials and trial results.